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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,986	07/01/2002	Seishi Nagamori	56972 (71526)	2684

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EXAMINER	
BROWN, TIMOTHY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,986	NAGAMORI, SEISHI	
	Examiner	Art Unit	
	Timothy M. Brown	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-11,13-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-11,13-16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *See Office Action*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication faxed on April 22, 2005. Claims 1, 2, 4, 6-11, 13-16 and 18 are pending while claims 3, 5, 12, 17 and 19 and 20 have been canceled.

Election/Restrictions

The restriction requirement as to Groups I and II is withdrawn in view of Applicant's amendment and remarks. Accordingly, claims 1, 2, 4, 6-11, 15, 16, and 18 are under examination while claims 13 and 14 are withdrawn. The invention under examination is a method for proliferating a hepatitis C virus (HCV) comprising the steps of placing a porous carrier in a culture vessel and streaming culture medium from the periphery of the culture vessel to the center of the culture vessel.

Priority

Receipt is acknowledged of the papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The specification is objected to because it fails to cross-note the international application upon which this application's priority is based. Applications that claim the benefit of a prior filed international application that designates the United States must contain a reference to each

such prior-filed application. The reference to the international application must contain the international application number and the international filing date. (MPEP 202.01).

Drawings

The drawings are objected to because they fail to refer to figure numbers and reference characters in English. Corrected drawings are required.

Information Disclosure Statement

The information disclosure statements submitted February 20, 2002 and February 28, 2003 have been considered. It should be noted that the information disclosure statement filed February 28, 2003 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each publication listed that is not in the English language. It has been placed in the application file, but the references that have been redacted from the attached Form 1449 have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6-11, 15, 16, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the structure of the culture vessel and media stream is not defined. Claim 1 recites "providing a porous carrier . . . in a culture vessel and streaming a liquid culture medium from periphery, bottom or upper side of the culture vessel toward the opposite side . . . ." However, there is no claim language that describes how the periphery, bottom and upper sides are connected such that one skilled in the art could understand how the media stream is introduced into the culture vessel.

Claim 1 is also indefinite in the recitation of "upper" (line 3) in that "upper" is a relative term of degree (see MPEP 2173.05(b)). Appropriate correction is required unless Applicant can point to a definition of the term "upper" in the specification that would clarify, to one of ordinary skill in the art, the scope of the claimed invention.

Claim 6 is indefinite in that the limitation "the flow of the liquid culture medium from around the periphery of the carrier" lacks antecedent basis.

Claim 7 is indefinite in the recitation of "allowing human hepatocyte. . . to permit a liquid culture medium to flow from the periphery . . . ." It is unclear how "allowing human hepatocyte" permits the liquid culture medium to flow from the periphery.

Claim 7 is also indefinite in the recitation of "placing therein a particulate porous carrier" because this language fails to distinctly state the nature of the particulate carrier. For example, it is unclear if and where the particulate carrier is attached to the culture vessel.

Claim 7 is also indefinite in that "toward" (line 5) is a relative term of degree.

Claim 7 is indefinite for failing to include an essential step. Claim 7 is drawn to "[a] method for proliferating a hepatitis C virus" using human hepatocytes. Yet, claim 7 fails to

include a step wherein the human hepatocytes are infected with HCV. Claim 7 therefore omits an essential step.

Finally, claim 7 is indefinite in that "the periphery of the main bioreactor unit" lacks antecedent basis.

Claim 10 is indefinite in that "the infection with hepatitis C virus" lacks antecedent basis.

Claim 11 is indefinite in that the following limitations lack antecedent basis: "the supply velocity of [the] fresh one of the culture medium;" and "the supply velocity of [the] oxygen."

Claim 11 is also indefinite in that it is unclear which velocities the claim is referring to when it recites "more than those velocities."

Claim 15 is indefinite in that "toward" is a relative term of degree.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 6-8, 15, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seipp et al. (J. Gen. Virol. (1997) Vol. 78, 2467-2476) in view of Takeshita et al. (In Vitro. Cell. Dev. Biol. (June 1998) Vol. 34, No. 6, 482-485).

Applicants invention is drawn to a method for proliferating HCV comprising the steps of placing a porous particulate carrier in a culture vessel, continually streaming a liquid culture medium from the periphery, bottom, or upper side of the culture vessel toward the center of the vessel, immobilizing and proliferating human hepatocytes on the porous carrier, and allowing the human hepatocytes to be infected with, and proliferate, HCV. The invention further provides, *inter alia*, that the human hepatocytes may be from an established cell line.

Seipp et al. dislose many features of the claimed invention including, culturing an established human hepatocyte cell line (HuH7 or HepG2) to establish a human hepatocyte culture, maintaining the human hepatocyte culture for several rounds of replication, infecting the human hepatocyte culture with HCV, and collecting infectious HCV produced by the infected human hepatocyte culture (*see e.g.* abstract; p. 2468; and Figs. 2-3). The only inventive feature that Seipp et al. does not disclose is immobilizing the human hepatocytes on a porous particulate carrier, and culturing the hepatocytes by continuously streaming a liquid culture medium from the periphery, bottom, or upper side of the culture vessel toward the center of the vessel. However, Takeshita et al. overcome this deficiency by disclosing a method for the three-dimensional culture of hepatocytes using continuously flowing medium. According to Takeshita et al., hepatocytes are fixed to a porous carrier, the porous carrier is placed in a reaction vessel, and liquid medium is streamed over the porous carrier and the hepatocytes thereby allowing the hepatocytes to proliferate (*see* abstract, "Materials and Methods" p. 482; and Fig. 1). Takeshita

et al. further disclose that their three-dimensional culture method is advantageous over mono-layer cell culture in that it provides long-term cell survival through increased oxygenation and a larger reservoir of continually circulating nutrients (p. 484, ¶ 2). Not only would these advantages motivate one skilled in the art to culture Seipp et al.'s HCV-infected human hepatoctyes using Takeshita et al.'s hepatocyte culture method, they would also provide one skilled in the art with a reasonable expectation of success using such a combination. Therefore, at the time of Applicant's invention, it would have been obvious to one of ordinary skill in the art to modify Seipp et al. with the teachings of Takehita et al. in order to improve the propagation of Seipp et al.'s HCV-infected human hepatocytes.

Claims 1, 2, 4, 6-11, 15, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seipp et al. (J. Gen. Virol. (1997) Vol. 78, 2467-2476) in view of Kawada et al. (In Vitro Cell. Develop. Biol. Anim. (February 1998) Vol. 34, 109-115).

As noted above, Seipp et al. teach all the features of the inventive method except for immobilizing the human hepatocytes on a porous particulate carrier, and culturing the human hepatocytes by continuously streaming a liquid culture medium from the periphery, bottom, or upper side of the culture vessel toward the center of the vessel. However, Kawada et al. overcome this deficiency by disclosing a radial flow bioreactor for culturing human hepatocytes. According to Kawada et al., human hepatocytes are cultured in a liquid media that is continuously circulated from the periphery of the bioreactor, in toward the bioreactor's central axis (see Abstract and Fig. 2). Kawada et al. expressly suggest using the radial flow bioreactor for culturing HCV-infected cells because they teach their radial flow bioreactor improves cell

lifespan, enhances cell density, and improves the ability to scale up hepatocyte populations. Moreover, Kawada et al. teach that human hepatocytes grown in the radial flow bioreactor maintain their hepatic function based on albumin production (Fig. 6). Thus, one skilled in the art could reasonably expect Seipp et al.'s HCV-infected hepatocytes to grow and propagate HCV. Given this expectation of success, and the stated benefits of the radial flow bioreactor, it would have been obvious to one skilled in the art to combine the teachings of Seipp et al. and Kawada et al. in order to arrive at the claimed invention.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

i. Zhang et al. (US 6,194,191 B1) Method for the production and purification of andenoviral vectors

ii. Naughton et al. (US 6,218,182) Method for culturing three-dimensional tissue in diffusion gradient bioreactor and use thereof

iii. Kino, Y. "Multiprous Cellulose Microcarrier for the Development of a Hybrid Artificial Liver Using Isolated Hepatocytes" J. Surg. Res. (1998) Vol. 79, 71-76

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy M. Brown whose telephone number is (571) 272-0773. The examiner can normally be reached on Monday - Friday, 8am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Timothy M. Brown
Examiner
Art Unit 1648

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